MEETING OF THE RADIOLOGICAL DEVICES PANEL

December 16, 1999

OPEN SESSION

Doubletree Hotel
Plaza Ballroom
1750 Rockville Pike
Rockville, Maryland

Participants in the Radiological Devices Panel Meeting
December 16, 1999

Voting Members

Brian S. Garra, M.D.
Chair

Judy M. Destouet, M.D.

James B. Smathers, Ph.D.

Arnold W. Malcolm, M.D.

A. Patricia Romilly-Harper, M.D.

Alicia Y. Toledano, Sc.D.

Steven E. Harms, M.D.

Temporary Voting Member

Wendie Berg, M.D., Ph.D.

Nonvoting Member

Marilyn R. Peters, M.N., M.P.H.
Consumer Representative

Temporary Nonvoting Members

Raymond P. Silkaitis, Ph.D.
Temporary Industry Representative

Open Public Hearing Speakers

Morgan Nields
Fischer Imaging Corporation

Daniel Kopans, M.D.
Massachusetts General Hospital

Earl Steinberg, Ph.D.
Covance Health Economics & Outcomes Services

Sponsor Representatives
GE Medical Systems

Scott Donnelly

R. Edward Hendrick, Ph.D.

FDA Participants

David Feigal, M.D., M.P.H.
Director, Center for Devices and Radiological Health

Daniel Schultz, M.D.
Director, Division of Reproductive, Abdominal, and Radiological Devices

Robert J. Doyle
Panel Executive Secretary

John Monahan
PMA Lead Reviewer

Robert Gagne, Ph.D.

Harry Bushar, Ph.D.

Robert F. Wagner, Ph.D.

William Sacks, Ph.D., M.D.

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Panel Chair **Dr. Brian S. Garra** opened the meeting at 8:40 a.m., noting that the voting members present constituted a quorum and asking all members to introduce themselves. Executive Secretary Robert Doyle read the conflict of interest statement and noted that Dr. Smathers had been granted a waiver allowing his participation. Matters unrelated to the panel discussion involving Dr. Garra had been considered, and his full participation was allowed. He also read an appointment to temporary voting status for Dr. Wendie Berg. Mr. Doyle announced two tentative future panel meeting dates: February 7, and May 15, 2000.

OPEN PUBLIC HEARING

Mr. Morgan Nields of Fischer Imaging Corporation asked the panel to consider improvements to the premarket approval (PMA) process. He offered as a case study his company's experience in trying to gain approval for a digital mammography device. He suggested several approaches to the regulatory dilemma, such as labeling for diagnostic mammography only or using the Mammography Quality Standards Act (MQSA) regulations to measure performance of digital mammography systems. Mr. Nields suggested that if the data presented in the PMA complied with FDA policy letters requiring statistically significant studies such as ground truth, sensitivity, and specificity or Receiver Operating Characteristic (ROC) analysis, then the application should be approved as a 510(k).

Dr. Daniel Kopans of Massachusetts General Hospital expressed his concern about the decision to require the PMA approval process for digital mammography. He noted that new film screening technology only requires 510(k)s and so should digital mammography. He stated that a large screening trial is not warranted and that direct image comparisons and physics studies

should suffice. He asked if the failure of the FDA to respond to legitimate questions raised by international experts could be motivated by politics, and he said that those involved in decision making should speak up. He recommended that the regulatory pathway should be via a 510(k).

OPEN COMMITTEE DISCUSSION

Dr. David Feigal, director of the Center for Devices and Radiological Health, presented plaques and letters of recognition to retiring panel members Dr. Smathers and Dr. Destouet for their years of participation on the panel.

Dr. Feigal also discussed the difficulty in determining a regulatory pathway for a screening device for a healthy population. He stated that the initial idea of an agreement paradigm or approach using a 510(k) pathway was changed to a PMA because the agency wanted the substantial data amassed by manufacturers to be compiled into a PMA. The 510(k) route is still open, as is a PMA route with data and a postmarket commitment. He stressed that the day's meeting should not be viewed as a paradigm for all other companies; the FDA's goal is to get products into the marketplace and to allow as many regulatory options as possible.

Dr. Dan Schultz, acting director of DRARD, gave an update on digital mammography's status and a brief history of the regulatory approach, from the agreement study approach as an alternative to large screening trials, to the realization that the agreement paradigm as proposed was not successful. He noted that letters to sponsors had suggested alternate pathways such as the PMA, and that revised guidance would be available in early 2000.

Dr. Schultz noted that mammography is different because it is the only imaging technology currently indicated for both diagnosis and screening and is relied upon by millions of women for early detection of breast cancer. He noted that in the past the Agency considered

perfect agreement as mimicking ground truth, but that now anything less than perfect agreement raises questions. Dr. Schultz discussed enriched trials versus screening trials, in which enriched trials provide adequate information for the diagnostic component of mammography and some information on screening, but screening trials are a more sensitive means to measure the ability to detect the earliest lesions. He listed the differences between the PMA and the 510(k) approach, noting that the PMA labeling can be tailored to reflect individual device data and may provide a faster route to market while still maintaining adequate regulatory control, although the 510(k) remains an option. Dr. Schultz concluded by listing three questions about PMA data, labeling, and developmental plan for the panel to consider.

Sponsor Presentation—PMA 990066 for GE Medical System's Senographe 2000D Full Field Digital Mammography System

Mr. Scott Donnelly gave an introduction and overview to Full Field Digital Mammography (FFDM), noting that the device uses established software and is currently approved for use in Europe and Asia. He read the indications for use and described the device components and working principles. Mr. Donnelly also summarized the nonclinical study results, with particular emphasis on detective quantum efficiency (DQE).

Dr. R. Edward Hendrick summarized the clinical studies, noting that the goal was to establish the safety and effectiveness of FFDM for screening and diagnosis of breast cancer. He presented data on the study cohort such as inclusion and exclusion criteria, patient demographics, and imaging techniques. He discussed results of reader studies numbers 1 and 2, as well as a result of a side-by-side analysis, noting that no adverse consequences (serious or otherwise) were reported during these PMA studies. The first two studies involved FFDM and Screen Film

Mammography (SFM) images of more than 600 subjects each, with both cancers and noncancers, which were read by two or more readers. The side-by side study analyzed 40 cancer cases by 5 independent readers to compare lesion conspicuity, chest-wall tissue inclusion and skin-line tissue visibility with the two modalities.

Dr Hendrick looked at differences between the studies and analyzed recall rates, sensitivity, and ROC curve areas. Study conclusions were that in both reader studies, recall rates demonstrate that FFDM recalls fewer women than SFM. In both studies, the sensitivity of FFDM is comparable to that of SFM for the detection of breast cancer. In both studies, ROC analysis shows that FFDM and SFM are comparable for breast cancer detection. Side-by-side feature analysis demonstrates that FFDM is comparable to SFM for lesion conspicuity and visibility of tissue at the chest wall, and that FFDM exceeds SFM for visibility of tissue at the skin line. Dr. Kendrick also outlined the roadmap for the immediate future, which begins with the approval of the hardcopy FFDM, then a PMA supplement for softcopy FFDM, and a postmarket approval study, which he outlined.

FDA Presentation

Mr. Jack Monahan, lead reviewer, introduced the PMA. He noted there were no major problems remaining with the manufacturing review and disinfection/sterilization procedures.

Dr. Robert Gagne gave the physics review of the PMA. He discussed what reviewers look for in terms of physics, general information, detected data, and displayed data. He defined detective quantum efficiency (DQE) and its relation to imaging performance and discussed quantum-limited operation in terms of noise components, quantum noise limited operation, and impact on DQE. He showed the relative DQE of the sponsor's FFDM device and SFM at three

different exposure values. In each case, up to 5 lp/mm (the Nyquist frequency for the digital detector) the FFDM was better. He also summarized key data from the PMA and concluded that the nonclinical studies provide important information on comparative imaging performance and system parameters such as DQE and quantum limited operation. He thought the information available in the device labeling was adequate and that the labeling will serve as a point of reference to the community.

Dr. Harry F. Bushar gave the statistical review, focusing on the second reader study. He explained the study procedure and analyzed specificity in terms of true negative and positive rates. He concluded that the sponsor's second reader study demonstrates that for patient management in a diagnostic population enriched with cancers selected from a screening study, FFDM specificity is not less than 5 percentage points lower than SFM specificity and FFDM sensitivity is not less than 10 percentage points lower than SFM sensitivity.

Dr. Robert F. Wagner presented an ROC analysis as related to the multiple reader study. He discussed the ROC paradigm on the probability of cancer or malignancy and sources of variability, referring to two classic papers on variability in mammography. He analyzed the multiple reader, multiple case (MRMC) ROC paradigm, and then discussed the sponsor's MRMC results. Dr. Wagner also presented the implications of the present variance structure for a postapproval trial drawn from a screening population assumed to have the same sampling properties as the current population but with different error bar widths.

Dr. William Sacks presented three subjects: side-by-side comparison, labeling, and the postapproval study. The side-by-side feature comparison, which was based on 40 cancers, focused on conspicuity of cancers, tissue near the chest wall, and visibility near the skin line. It

also compared the ability to discriminate between benign and malignant calcifications and the ability to detect fine marginal irregularities of masses. Dr. Sacks presented these comparisons using a Likert scale. He also presented a comparison of FFDM and SFM ROC areas, as well as sensitivity, and specificity with error bars. He suggested a postapproval study on the grounds that the premarket study was modest in size, which results in wide confidence intervals in the differences between FFDM and SFM. The premarket study was also performed in part on a diagnostic cohort, which may not fully test FFDM's ability to detect smaller, earlier cancers. He proposed a postapproval study design using a screening population and double exposing every subject to demonstrate noninferiority in ROC area, sensitivity, and specificity. It would use hard copy and analyze all cancers and randomly selected noncancers.

Panel Discussion

Dr. Judy Destouet, lead panel discussant, raised a number of questions for the sponsor. She raised issues of study design, noting that it was hard to compare the modalities because of reader variability. She also asked about the lower recall rate with the device, noting that the flexibility in positioning allows better visualization of lesions. Dr. Destouet suggested that one explanation for the differing ROC curves might be less confidence on the part of readers with the newer digital modality, a shortcoming of the reader rather than the modality. She suggested that the company use international data and was concerned about releasing the device in its least favorable light by using only the hard copy. Dr. Destouet stated that she thought the device would have wider patient acceptance, in part because of its shorter examination time. She also had a number of specific questions about the workstation platforms and image processing.

FDA Questions

The panel agreed that there were sufficient data to conclude that the device is safe and effective. On labeling, the panel thought the clinical data should be fully included in the application. There was panel concern over the mechanism for approval in that the PMA does not fully demonstrate screening but focuses on interpretation rather than data gathering. It was stated that the indication was appropriate, but that the PMA mechanism might not address it. Dr. Garra stated that the labeling is a truncated version of the study data and should be modified and summarized to show the difference between this study and a true screening study. It should be noted that this population was a diagnostic and a screening population, but the study was run in a screening mode. It was recommended that the sponsor collect some applicable international screening data because it is hard to get true screening data in the United States.

The panel discussed a number of issues that could be included in a postmarket study. One suggestion was to describe variability among mammographers, although it was noted that this is not device-driven. One panel member suggested that it would be costly to prove device effectiveness as a screening tool when the technique is likely to turn out equally effective as SFM over time in any case. A small diagnostic trial in diagnostic mode was suggested, with a magnification mode to be determined. It was suggested that the company explore the possibility of having readers use the U.S. Army data to solidify sample numbers and then determine whether an additional study needs to be made. There was some panel disagreement over whether the appropriate model is the Pap screening reader example or the use of digital techniques in other fields. The need to incorporate innovations without locking the company into a rigid process was stressed because the technology is rapidly evolving with new information constantly being

published. Several members urged that the soft copy approval should not be a major hurdle and should be included or incorporated as soon as possible without major regulatory hurdles.

OPEN PUBLIC HEARING

Dr. Earl Steinberg, from Covance Health Economics & Outcomes Services and representing Fuji Medical Systems, stated that he was pleased that the FDA appeared to realize the noninferiority of digital mammography but he was concerned that the diagnostic mode may be different in a screening population than in a diagnostic population and that the study was not sufficiently powered to prove substantial equivalence in both screening and diagnostic populations. He suggested it be approved as technically substantially equivalent to SFM but with no reference to screening or diagnostic purposes.

Dr. Daniel Kopans, from Massachusetts General Hospital, stated that equivalence of FFDM and SFM was clearly established. He was concerned that the FDA was locked into a PMA process and locked into a postmarket study based on the faulty paradigm of the Pap smear reader. He thought a study requiring double exposure of subjects raises major concerns. He urged the panel to strongly support approval on the basis of demonstrated 510(k) equivalence and to improve this process by not requiring a demonstration of equivalence again in the future.

FDA Comment

It was noted that MQSA might provide useful information on the maximum allowed dosage through its safe radiation program.

Sponsor Comment

The sponsors thanked the panel for its comments, in particular on the postmarket study and soft copy recommendations.

Panel Recommendations and Vote

It was moved and seconded to recommend the PMA as approvable without conditions. This was followed by a recommendation that the manufacturer deploy the soft copy workstation to serve as an adjunct to hard copy. It was stated that further studies were not warranted at this time and were not a good use of resources. Panel members observed that the FFDM hard-copy technology was demonstrated as equivalent to SFM and actually probably beyond that point. Data can already be studied as part of the public record and should be made available to the FDA. An amendment was then made and seconded to add a one-paragraph Executive Summary to the clinical data in the labeling that emphasizes the differences between this study and a true screening study and shows how this study population differs from a true screening and true diagnostic population.

The FDA commented that they and the sponsors would work together to submit/approve soft copy as soon as possible. It was clarified that the panel is not recommending approval for soft copy but is recommending studies be done as soon as possible to expedite soft copy incorporation into the FFDM device. The panel emphasized the importance of the use of soft-copy for image interpretation.

The first motion was then withdrawn in favor of a motion to recommend the PMA as approvable with conditions as follows: 1) the manufacturer should deploy a soft copy workstation to serve as an adjunct to hard copy 2) an executive section in the front of the labeling should be inserted that emphasizes the difference between the study population and true screening and diagnostic populations and 3) approval of the soft copy modality should be expedited.

This motion was seconded and unanimously approved.

In concluding remarks, panel members stated that the device was a significant advance and that digital mammography approval should be expedited as soon as possible.

Executive Secretary Robert Doyle thanked the panel. Panel Chair Dr. Brian Garra thanked all participants in the meeting and adjourned the Open Session at 3:30 p.m.

I certify that I attended the Open Session of the Radiological Devices Panel Meeting on December 16, 1999, and that this summary accurately reflects what transpired.

Robert J. Doyle
Executive Secretary

I approve the minutes of the meeting as recorded in this summary.

11 JAN 2000

Dr. Brian Garra
Chair

Summary minutes prepared by Aileen M. Moodie
9821 Hollow Glen Pl.
Silver Spring, MD 20910
301-587-9722